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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/837,217	04/19/2001	Chia Ning (Sophia) Chang	01779784	6921

7590 05/13/2003

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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/13/2003

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/837,217	CHANG, CHIA NING (SOPHIA)	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *9 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' amendment filed on March 05, 2003 in Paper No. 12 has been entered.

Claims 1-10 are pending in the present application.

This application contains claims 9-10 drawn to an invention nonelected with traverse in Paper No. 8. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Amended claims 1-8 are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior Office Action.

Response to Amendment

The rejection under 35 U.S.C. § 112, first paragraph, is withdrawn in light of Applicants' amendment.

Specification

In the Brief Description of the Drawings Section, Fig. 2, 3, 4, 5, 7, 8, 9, 13, 14, 15, 16 are referred. However, Fig. 2A-B, 3A-B, 4A-B, 5A-D, 7A-C, 8A-B, 9A-C, 13A-B, 14A-B, 15A-B and 16A-C are submitted. Appropriate correction is requested.

Following is a new ground of rejection necessitated by Applicants' amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 recites the limitation "the BMP-2 gene" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim. Therefore, the metes and bounds of the claim are not clearly determined.

Claim Rejections - 35 USC § 102

Amended claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Moutsatsos et al. (WO99/11664).

The claims are drawn to a pharmaceutical composition for topical application at a site requiring new bone, cartilage or connective tissue formation in a subject, comprising a plurality of bone marrow stromal cells comprising a vector comprising a DNA sequence encoding BMP-2 operably linked to a promoter, and a pharmaceutically acceptable polymer; the same composition wherein the polymer is alginate or collagen.

Moutsatsos et al. disclose the preparation of cells (cell lines or primary cells including bone marrow stromal cells) transformed with a recombinant vector (including viral vectors such as adenovirus and retrovirus) expressing one or more bone morphogenetic proteins (BMPs, including human BMP-2) or growth and differentiating

factors (GDSs) for regeneration of bone formation *in vivo* (see example 14, pages 41-50). Moutsatsos et al. also teach that the recombinant cells can be administered in combination with an appropriate matrix for supporting the composition, and this matrix can be in the form of biocompatible matrix biomaterials (a pharmaceutically acceptable polymer) including polylactic acid, polyanhydrides, calcium sulfate, bone, dermal collagen, hydroxyappatite, aluminates, pure proteins or extracellular matrix components and others (line 32 on page 6 continues to line 27 on page 7). Furthermore, Moutsatsos et al. teach that their delivery system for rhBMP-2 can be applied locally or regionally (see examples 13-14; particularly page 41, lines 15-17 and line 34 of page 45 continues to line 2 of page 46).

Accordingly, Moutsatsos et al. (WO99/11664) anticipate the instant claims.

Amended claims 1-2, 4-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Riew et al. (Calcif. Tissue Int. 63:357-360, 1998) as evidenced by Caplan et al. (U.S. 5,855,619).

Riew et al. teach the preparation and transduction of rabbit bone marrow mesenchymal stem cells isolated from bone marrow cells, with a recombinant adenoviral vector expressing human BMP-2 for transplantation in a rabbit spinal fusion model (see Materials and Methods on page 358). Riew et al. further teach that the transfected cells were harvested and resuspended in collagen solution (Pancogene S) at 3 x 10^6 cells/ml for autologous implantation into the L5/L6 interspace of rabbits from which the bone marrow cells were harvested 4 weeks earlier (page 358, under sections

titled "Human BMP-2 protein expression in MSC cells" and "Rabbit spine fusion model"). Riew et al. further demonstrate that new bone formation occurs at the site of autologous implantation of Adv-BMP2 transduced mesenchymal stem cells in one of the treated animals (Figs. 2-4). Pancogene S is a trademark for a sterilized type I collagen solution from Gattefosse SA as evidenced by the teachings of Caplan et al. (col. 4, lines 64-65). Since a plurality of bone marrow stromal cells transformed or transfected with a recombinant adenovirus expressing human BMP-2 of the instant claims encompass a population of bone marrow mesenchymal stem cells transfected with a recombinant adenovirus expressing human BMP-2 taught by Riew et al., coupled with the same method steps and a treated rabbit as a subject, the reference anticipates the instant claims.

Amended claims 1-2, 4-7 are rejected under 35 U.S.C. 102(a) as being anticipated by Cheng et al. (Calcif. Tissue Int. 68:87-94, 2001) as evidenced by Caplan et al. (U.S. Patent No. 5,855,619).

Cheng et al. teach the preparation and transduction of rabbit bone marrow mesenchymal stem cells isolated from bone marrow cells, with a recombinant adenoviral vector expressing human BMP-2 for transplantation in a rabbit spine fusion model (see Materials and Methods on page 88). Cheng et al. further teach that the transfected cells were harvested and resuspended in collagen solution (Pancogene S) at 3 x 10^6 cells/ml for autologous implantation into the L5/L6 interspace of rabbits from which the bone marrow cells were harvested 4 weeks earlier (page 88, col. 2, under

sections titled "Transducing rabbit bone marrow mesenchymal stem cells with Adv-BMP2" and "Rabbit spine fusion model"). Pancogene S is a trademark for a sterilized type I collagen solution from Gattefosse SA as evidenced by the teachings of Caplan et al. (col. 4, lines 64-65). Cheng et al. further demonstrate that new bone formation occurs at the site of autologous implantation of Adv-BMP2 transduced mesenchymal stem cells. Since a plurality of bone marrow stromal cells transformed or transfected with a recombinant adenovirus expressing human BMP-2 of the instant claims encompass a population of bone marrow mesenchymal stem cells transfected with a recombinant adenovirus expressing human BMP-2 taught by Cheng et al., coupled with the same method steps and a treated rabbit as a subject, the reference anticipates the instant claims.

Response to Arguments

Applicants' arguments related to the above rejections in the Amendment filed on March 05, 2003 in Paper No. 12 have been fully considered.

Applicants argue mainly that none of the references cited above (Moutsatsos et al., Riew et al. and Cheng et al.) teaches or suggests pharmaceutical compositions for topical application or methods of enhancing new bone, cartilage or connective tissue formation in a subject requiring topical application of BMP-2 producing MSCs. Therefore, none of the cited references anticipates the presently claimed invention. Applicants' arguments are respectfully found to be unpersuasive because according to Webster's Dictionary the term "topical" means pertinent to a place or concerning local

matters (see attachment). Therefore, the teachings of Moutsatsos et al. (e.g., their delivery system for rhBMP-2 can be applied locally or regionally, see examples 13-14; particularly page 41, lines 15-17 and line 34 of page 45 continues to line2 of page 46) and Riew et al. and Cheng et al. (e.g. autologous implantation of mesenchymal stem cells expressing rhBMP-2 into the L5/L6 interspace of rabbits) meet the limitation of topical application.

Claim Rejections - 35 USC § 103

Amended claims 1 and 3-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moutsatsos et al. (WO99/11664) in view of Riew et al. (Calcif. Tissue Int. 63:357-360, 1998) or Cheng et al. (Calcif. Tissue Int. 68:87-94, 2001).

Moutsatsos et al. disclose the preparation of cells (cell lines or primary cells including bone marrow stromal cells) transformed with a recombinant vector (including viral vectors such as adenovirus and retrovirus) expressing one or more bone morphogenetic proteins (BMPs, including human BMP-2) or growth and differentiating factors (GDSs) for regeneration of bone formation via *in vivo* or *ex vivo* gene therapy (see example 14, pages 41-50). Moutsatsos et al. also teach that the recombinant cells can be administered in combination with an appropriate matrix for supporting the composition, and this matrix can be in the form of biocompatible matrix biomaterials (a pharmaceutically acceptable polymer) including polylactic acid, polyanhydrides, calscium sulfate, bone, dermal collagen, hydroxyappatite, aluminates, pure proteins or extracellular matrix components and others (line 32 on page 6 continues to line 27 on

page 7). Furthermore, Moutsatsos et al. teach that their delivery system for rhBMP-2 can be applied locally or regionally (see examples 13-14; particularly page 41, lines 15-17 and line 34 of page 45 continues to line 2 of page 46).

Moutsatsos et al. do not specifically teach an autologous implantation method using a plurality of bone marrow stromal cells transformed or transfected with a recombinant vector expressing BMP-2 from a subject even though Moutsatsos et al. teach the implantation of collagen gels containing marrow stromal cells infected with a recombinant adenovirus expressing human BMP-2 into syngeneic mice (see example 14). Moutsatsos et al. also do not teach how to make and use a composition comprising bone marrow stromal cells transfected with a recombinant adenovirus expressing human BMP-2 at a concentration of 50 x 10^6 cells per ml of a pharmaceutically acceptable polymer.

At the effective filing date of the present application, both Riew et al. and Cheng et al. already teach the preparation and transduction of autologous rabbit bone marrow mesenchymal stem cells isolated from bone marrow cells, with a recombinant adenoviral vector expressing human BMP-2 for transplantation in a rabbit spinal fusion model (see Materials and Methods section). Both Riew et al. and Cheng et al. further teach that the transfected cells were harvested and resuspended in collagen solution (Pancogene S, which is a Trademark for a sterilized type I collagen solution from Gattefosse SA) at 3x 10^6 cells/ml for autologous implantation into the L5/L6 interspace of rabbits from which the bone marrow cells were harvested 4 weeks earlier. Both Riew et al. and Cheng et al. further demonstrate successfully that new bone formation occurs

at the site of autologous implantation of Adv-BMP2 transduced mesenchymal stem cells in the treated animals.

Accordingly, it would have been obvious and within the scope of skill for an ordinary skill artisan to modify the composition and method taught by Moutsatsos et al. (WO99/11664) by using harvested autologous mesenchymal stem cells from bone marrow or bone marrow cells, that have been transfected with a recombinant vector expressing human BMP-2 for induction of bone formation at a desired site in a subject in need thereof, in light of the teachings of Riew et al. or Cheng et al. It would also have been obvious that the transfected BMP-2 protein producing mesenchymal stem cells can be formulated in Pancogen S polymer, an appropriate matrix that has been utilized by both Riew et al. and Cheng et al. for supporting the transfected cells for bone induction *in vivo*. Additionally, it would also have been obvious for one of ordinary skilled artisan to utilize various concentrations of the transfected mesenchymal stem cells in a collagen solution, including the concentration of 50×10^6 transfected cells per ml of a pharmaceutically acceptable polymer for optimizing the desired degree of bone formation *in vivo*.

An ordinary skilled artisan would have been motivated to make the above modifications because an increased in the concentration of implanted mesenchymal stem cells transfected with a recombinant adenovirus expressing human BMP-2 would result in an increase in differentiated osteoblasts as well as the amount of secreted human BMP-2 at the implanted site to increase bone formation as required. Furthermore, one of ordinary skilled artisan would have been motivated to use

autologous mesenchymal stem cells from bone marrow or bone marrow cells, that have been transfected with a recombinant vector expressing human BMP-2 for induction of bone formation at a desired site in a subject in need thereof to minimize any adverse host immune responses against the transplanted cells, which is recognized by Moutsatsos for the teaching of implantation of collagen gels containing marrow stromal cells infected with a recombinant adenovirus expressing human BMP-2 into syngeneic mice (see example 14).

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Amended claims 1, 3, 5 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Riew et al. (Calcif. Tissue Int. 63:357-360, 1998) or Cheng et al. (Calcif. Tissue Int. 68:87-94, 2001).

Both Riew et al. and Cheng et al. teach the preparation and transduction of rabbit bone marrow mesenchymal stem cells isolated from bone marrow cells, with a recombinant adenoviral vector expressing human BMP-2 in a rabbit spinal fusion model (see Materials and Methods section). Both Riew et al. and Cheng et al. further teach that the transfected cells were harvested and resuspended in collagen solution (Pancogene S) at 3 x 10^6 cells/ml for autologous implantation into the L5/L6 interspace of rabbits from which the bone marrow cells were harvested 4 weeks earlier. Both Riew et al. and Cheng et al. further demonstrate successfully that new bone formation occurs at the site of autologous implantation of Adv-BMP2 transduced mesenchymal stem

cells. It is noted that a plurality of bone marrow stromal cells transformed or transfected with a recombinant adenovirus expressing human BMP-2 of the instant claims encompass a population of bone marrow mesenchymal stem cells transfected with a recombinant adenovirus expressing human BMP-2 taught by both Riew et al. and Cheng et al.

Neither Riew et al. nor Cheng et al. teach a composition wherein the bone marrow stromal cells expressing BMP-2 are present in a concentration of about 50 x 10^6 per ml of a pharmaceutically acceptable polymer, and a method of using the same.

However, at the effective filing date of the present application it would have been obvious and within the scope of skill for an ordinary skill artisan to modify the composition and the method taught by Riew et al. or Cheng et al. by using a higher concentration of the transfected mesenchymal stem cells in a collagen solution, including the concentration of 50 x 10^6 transfected cells per ml of a pharmaceutically acceptable polymer, for optimization the desired degree of bone formation *in vivo*.

An ordinary skilled artisan would have been motivated to make the above modification because an increased in the concentration of implanted mesenchymal stem cells transfected with a recombinant adenovirus expressing human BMP-2 would result in an increased in differentiated osteoblasts as well as the amount of secreted human BMP-2 at the implanted site to increase bone formation.

Therefore, the claimed invention as a whole was *prima facie* obvious.

Response to Arguments

Applicants' arguments related to the above rejections in the Amendment filed on March 05, 2003 in Paper No. 12 have been fully considered.

Applicants argue mainly that none of the references cited above (Moutsatsos et al., Riew et al. and Cheng et al.) teaches or suggests pharmaceutical compositions for topical application or methods of enhancing new bone, cartilage or connective tissue formation in a subject requiring topical application of BMP-2 producing MSCs. Applicants' arguments are respectfully found to be unpersuasive because according to Webster's Dictionary the term "topical" means pertinent to a place or concerning local matters (see attachment). Therefore, Moutsatsos et al. (e.g., their delivery system for rhBMP-2 can be applied locally or regionally, see examples 13-14; particularly page 41, lines 15-17 and line 34 of page 45 continues to line 2 of page 46), Riew et al. and Cheng et al. (e.g. autologous implantation of mesenchymal stem cells expressing rhBMP-2 into the L5/L6 interspace of rabbits) do teach the limitation of topical application.

Accordingly, claims 1 and 3-8 are rejected for the reasons set forth above.

Conclusions

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (703) 308-1906, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER